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CLINICAL TRIAL REPORT

Adjuvant Lenvatinib for High-Risk CNLC IIb/IIIa Hepatocellular Carcinoma After Curative Hepatectomy: A Prospective Exploratory Study

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Objective: The risk of hepatocellular carcinoma (HCC) recurrence following surgical resection remains high, approaching 50%-70% at 5 years, with the highest risk occurring in the first year after resection. This study aimed to evaluate the efficacy and safety of lenvatinib as adjuvant therapy for HCC.

Methods: In this open-label, single-arm, prospective, multicenter Phase II clinical study, a total of 51 hCC patients with China Liver Cancer (CNLC) stage IIb/IIIa (ie tumor number ≥ 4 or vascular invasion, equivalent to BCLC B/C) who underwent R0 resection 4–6 weeks after curative surgery were enrolled. Patients received lenvatinib for up to 12 months, at a dose of 8 mg/day for body weight < 60 kg, or 12 mg/day for ≥ 60 kg. Patients were followed up every 2 months for a median of 24.1 months.

Results: The median recurrence-free survival (RFS) was 16.1 months, with a 12-month RFS rate of 60.4%, exceeding the historical rate of under 50% in similar high-risk populations. The 12-month overall survival (OS) rate was 93.6%, while median OS was not reached. Treatment-related adverse events (TRAEs) occurred in 88.0% of patients, with ≥ grade 3 TRAEs in 14.0%, including thrombocytopenia and proteinuria in 6.0% of patients each, and leukopenia, neutropenia, elevated aspartate aminotransferase, and elevated alanine aminotransferase in 2.0% of patients each. AEs leading to the interruption of lenvatinib occurred in 6.0% of patients, and dose reduction was required in 18% of patients. No deaths were observed.

Conclusion: Lenvatinib may be an effective adjuvant therapy for patients with CNLC stage IIb/IIIa HCC after R0 hepatectomy. However, the findings are limited by the single-arm design and small patient cohort, necessitating larger randomized controlled trials for validation.

Keywords: lenvatinib, hepatocellular carcinoma, recurrence, adjuvant therapy

Introduction

Primary liver cancer is one of the most common malignant tumors of the digestive system and the second leading cause of cancer death worldwide, including in China.[1,2] The annual incidence and mortality rates of liver cancer in China account for more than half of the global figures.[3–5] Hepatocellular carcinoma (HCC), the most common pathological type of primary liver cancer, represents 75% to 85% of cases, posing a serious threat to human health.[5,6]

Hepatic resection is the mainstay of curative treatment for HCC, especially for early- to mid-stage HCC. However, the high invasiveness of HCC leads to significant postoperative recurrence, with 5-year postoperative recurrence rates reaching 50% to 70%,[7,8] severely impacting long-term survival. In China, the overall postoperative prognosis of HCC patients with China Liver

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Cancer (CNLC) stage IIb/IIIa (equivalent to BCLC B/C, characterized by tumor number ≥ 4 or vascular invasion) remains unsatisfactory due to the high incidence of recurrence. Specifically, the one-year postoperative recurrence rates for CNLC IIb and IIIa patients are 62.5% and 78.3%, respectively,[9] which are higher than those observed in early-stage patients. These data underscore an important unmet medical need for enhanced postoperative surveillance and the development of effective adjuvant therapeutic strategies to improve recurrence outcomes in high-risk CNLC IIb/IIIa patients.[10,11]

Several studies on adjuvant therapies for HCC has explored different strategies to reduce intrahepatic and extrahepatic recurrence.[12] The Phase III STORM study showed that sorafenib, administered as a systemic adjuvant therapy for a median duration of 12.5 months, failed to improve recurrence-free survival (RFS) and overall survival (OS) in early-stage patients (BCLC stage A) after radical treatment.[13] Recent studies have focused mainly on early-stage patients (BCLC stage A), but there is limited data available on CNLC stage IIb/IIIa. Donafenib plus toripalimab for six months after resection showed a one-year RFS rate of 80% in BCLC stage A-B patients with high-risk factors, while the median RFS was not reached.[14] In the IMbrave050 trial of predominantly BCLC stage A (> 80%) patients, adjuvant atezolizumab plus bevacizumab initially showed improved 1-year RFS (78% vs 65%) versus active surveillance,[15] but with longer follow-up, this benefit was not maintained.[16]

Vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) pathways are crucial in cancer cell growth and are highly expressed in advanced HCC tumors.[17] Lenvatinib is an oral multi-kinase inhibitor that targets VEGFR1-3, FGFR1-4, PDGFα, RET, and KIT,[18,19] exhibiting a lower IC_{50} than sorafenib, which inhibits VEGFR1-3, PDGFRβ, Flt-3, KIT, RET.[20] With a stronger inhibitory effect on VEGF and FGF pathways,[21] lenvatinib's dual pathway inhibition may offer advantages in high-risk patients, where micrometastases are likely present but undetectable at surgery,[17] by suppressing these micrometastases and potentially delaying recurrence.The REFLECT study demonstrated that lenvatinib was non-inferior to sorafenib for first-line treatment unresectable HCC(uHCC),[22] with a median OS (mOS) (13.6 vs 12.3 months, HR = 0.92, 95% CI 0.79–1.06). Moreover, lenvatinib significantly improved median PFS (mPFS) (7.4 vs 3.7 months), time to progression (mTTP) (8.9 vs 3.7 months), and overall response rate (ORR) (40.6% vs 12.4%) ($P < 0.0001$). The safety profiles of lenvatinib and sorafenib were comparable, with similar rates of treatment-related adverse events (TRAEs) and discontinuations (9% vs 7%, respectively). Based on these findings, lenvatinib was approved in 2018 by EMEA, FDA, and NMPA for first-line treatment of uHCC.

Considering that micrometastases are likely present at the time of surgery in high-risk patients, and given lenvatinib's dual VEGFR/FGFR inhibition, particularly FGFR's role in targeting residual micrometastases,[18] this study investigated its use as adjuvant therapy in Chinese HCC patients, aiming to improve 1-year RFS with 12 months of post-surgical treatment.

Materials and Methods

Trial Design

This was an open-label, single-arm, prospective, multicenter phase II study. This study was carried out in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All patients gave written informed consent to participate in the study. Protocol approval was obtained from the Institutional Review Board (IRB) or Ethics Committee (EC) at each site. The first EC approval for this study was granted on December 19, 2019, from Zhongshan Hospital, Fudan University, Shanghai, China (approval number: B2019-272R). This study was registered on ClinicalTrials.gov (NCT04227808).

Participants

The subjects included in this study were patients with histologically diagnosed HCC. The main inclusion criteria included: CNLC stage IIb/IIIa (ie tumor number ≥ 4 or vascular invasion, equivalent to BCLC B/C) HCC, confirmed R0 resection (microscopic and macroscopic tumor clearance) 4–6 weeks after curative surgery, no residual tumor in the remnant liver, and no metastases in other organs confirmed by imaging tests (MRI/CT), 6 weeks or less from surgery to study entry, ECOG score of 0–1, Child-Pugh class A, and age 18–75 with no gender restriction. The main exclusion criteria included: 1) Hematology: absolute neutrophil count (ANC) < 1.5×10^9/L, hemoglobin (HB) < 80 g/L, platelet (PLT) < 75×10^9/L; 2) Coagulation: international normalized ratio (INR) > 2.3, or prothrombin time (PT) prolonged

> 6 seconds; 3) Liver function: serum albumin (ALB) < 2.8 g/dL, total bilirubin (TBIL) > 51.3 μmol/L, alkaline phosphatase or serum transaminase (ALT and AST) > 5 times the upper limit of normal (ULN); 4) Renal function: serum creatinine (CRE) > 1.5 times the ULN; 5) Hepatic portal lymph node metastases; 6) Presence of ascites, hepatic encephalopathy, Gilbert's syndrome, or sclerosing cholangitis.

Interventions

All patients received lenvatinib as adjuvant treatment for 12 months after enrollment. Patients weighing < 60 kg took lenvatinib orally at 8 mg/day, and those ≥ 60 kg took lenvatinib orally at 12 mg/day. Treatment was continued until tumor recurrence, intolerance, or death. No other anti-tumor drug was permitted during the study period. To manage treatment-emergent hypertension, we referred to a previous study.[23] Treatment interruptions or dose reductions were allowed in the event of other AEs. If patients experienced serious AEs, discontinuing the treatment was essential.

Outcome Measures

The primary endpoint was the 1-year RFS rate, defined as the proportion of patients who did not experience radiologically diagnosed disease recurrence (local, regional, or distant) or death by any cause within one year from enrollment, whichever occurred first. Intrahepatic recurrence was defined as the appearance of new intrahepatic lesions in accordance with American Association for the Study of Liver Diseases (AASLD) diagnosis guidelines, and extrahepatic recurrence was defined as per RECIST version 1.1. All radiological images were reviewed by the investigators and the radiologists at each site, based on which the RFS rate was calculated.

Secondary endpoints included: 1) OS, defined as the time from patient enrollment to death by any cause. 2) Safety evaluation, including AEs, serious AEs (SAEs), vital signs, physical examination, and abnormal laboratory tests. The severity of AEs was evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Sample Size

The sample size was calculated based on the 1-year RFS rate. A retrospective analysis of 10,966 Chinese patients with liver cancer showed that the recurrence rates for stages IIb and IIIa were 55.9% and 59.9%, respectively, corresponding to 1-year RFS rates of 44.1% and 40.1%.[24] Historical data indicates a 1-year RFS rate of 50%. Under the hypothesis that lenvatinib adjuvant therapy could increase the 1-year RFS rate to 70%, 44 subjects were needed for enrollment in a single-stage design with an α set at 0.05 and a power of 85%. If the number of subjects without recurrence or metastasis after one year was ≥ 28, the study was considered to have reached the primary endpoint. Considering a 10% drop-out rate, a total of 50 subjects needed to be enrolled.

Statistical Analysis

All enrolled patients who received at least one dose of lenvatinib and had at least one response evaluation were included in the full analysis set (FAS). Patients who completed the study treatment as specified in the protocol with no major protocol deviations and completed the primary response evaluation were included in the per-protocol set (PPS). The FAS was the main analysis set for response evaluation. All safety analyses were based on the safety set (SS), which included patients who signed the informed consent form, were enrolled, and received at least one dose of lenvatinib.

The Kaplan-Meier (KM) method was used to plot the RFS curve and estimate the median RFS to determine the 1-year RFS rate. The KM method was also used to plot the OS curve and estimate the median OS. Safety was analyzed descriptively, and all AEs were listed by patients, with the incidence of AEs, SAEs, deaths, and AEs leading to interruption during treatment being calculated. Programming and statistical analysis were performed using SAS9.4 and R4.3.0 software.

Results

Participants and Baseline Characteristics

Between April 2020 and January 2022, 59 patients from 4 sites were screened, and 51 were enrolled. Of these, 3 subjects were not included in the efficacy analyses due to violations of the eligibility criteria and the subsequent withdrawal, with one after the enrollment but before lenvatinib treatment and two after 2 or 4 days of lenvatinib treatment. Therefore, the efficacy analysis population consisted of 48 subjects in the FAS and PPS, and safety analysis population consisted of 50 subjects in the SS.

The baseline characteristics of the subjects are shown in Table 1. The median age was 56 years, and most patients were male (83%). Most (85%) patients had CNLC stage IIIa/BCLC stage C disease. HBV infection was the main

Table 1 Baseline Patient Demographics and Disease Characteristics

	Patients (n=48)
Age (years), median (range)	56 (26–75)
Gender	
Male	40 (83%)
Female	8 (17%)
ECOG performance status score	
0	41 (85%)
1	7 (15%)
CNLC stage at initial diagnosis	
Stage IIb (selected BCLC stage B)	7 (15%)
Stage IIIa (BCLC stage C)	41 (85%)
Longest diameter of the largest tumor at diagnosis (cm), median (range)	6.25 (2.20–15.00)
Any tumor ≥ 5 cm	
Yes	31 (65%)
No	17 (35%)
Number of tumors	
1	36 (75%)
2	5 (10%)
≥ 3	7 (15%)
Tumor thrombus involvement	
Macroscopic tumor thrombus	33 (69%)
Microvascular tumor thrombus	10 (21%)
None	5 (10%)
Microvascular invasion score	
M0	3 (6%)
M1	22 (46%)
M2	23 (48%)

(*Continued*)

Table 1 (Continued).

	Patients (n=48)
Vp class [16]	
0	10 (21%)
1	3 (6%)
2	22 (46%)
3	10 (21%)
4	3 (6%)
Structural integrity of HCC capsule	
Yes	14 (29%)
No	34 (71%)
HBV	
Positive	36 (75%)
Negative	12 (25%)
HCV	
Positive	8 (17%)
Negative	40 (83%)
Baseline AFP concentration (ng/mL)	
n (n missing)	48 (0)
Mean ± SD	163.55 ± 464.60
Median (range)	15.34 (2.00–2864.2)
Baseline AFP level n (%)	
≥ 400 ng/mL	3 (6.3%)
200–400 ng/mL	5 (10.4%)
< 200 ng/mL	40 (83.3%)
Preoperative AFP concentration (ng/mL)	
n (n missing)	47 (1)
Mean ± SD	4983.7 ± 11,180
Median (range)	476.00 (1.60–55,396)
Preoperative AFP level n (%)	
≥ 400 ng/mL	24 (51%)
200–400 ng/mL	3 (6%)
< 200 ng/mL	20 (43%)
Months from enrollment to surgery, median (range)	0.93 (0.07–2.53)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CNLC, China Liver Cancer; BCLC, Barcelona Clinic Liver Cancer; Vp class, Liver Cancer Study Group of Japan portal vein tumor thrombus (PVTT) classification; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; SD, standard deviation.

underlying cause of HCC (75%). Among these patients, the median tumor size, based on the longest diameter of the largest tumor at diagnosis, was 6.25 (range, 2.20–15.00) cm. Thirty-one (65%, 31/48) had tumors ≥ 5 cm, and 36 (75%, 36/48) had a solitary tumor. Microvascular invasion was reported in 45 (94%) of 48 resected tumors, and Vp1 or Vp2 portal vein invasion was noted in 25 (52.1%, 25/48), while Vp3 or Vp4 in 13 (27.1%, 13/48). Capsule integrity was lacking in 34 (71%, 34/48) patients. Most (83%) patients had baseline alpha-fetoprotein (AFP) level < 200 ng/mL, with a median AFP level of 15.34 ng/mL. More than half of the patients had an interval of less than 6 weeks between surgery and enrollment, with a median interval of 0.93 (range, 0.07–2.53) months.

Treatment Compliance

Among the 48 subjects included in the FAS, 14 (29%) received lenvatinib 8 mg/day, while 34 (71%) received lenvatinib 12 mg/day. The mean dose intensity was 10.83 ± 1.84 mg, and median duration of treatment was 11.83 (range, 1.71–13.15) months.

The 1-Year RFS Rate

At the clinical data cutoff on Jan 16, 2023, the median follow-up time was 24.1 months. A total of 28 patients (58%) of 48 experienced recurrence or died. As shown in Table 2, the median RFS was 16.1 months (95% CI 10.2- not available), and the 12-month RFS rate was 60.4% (95% CI 45.2% - 72.6%). The KM survival curve of RFS is shown in Figure 1.

As shown in Table 3, the 12-month RFS rate was 65.7% (95% CI 47.6%-78.9%) for patients with Vp class 0–2, 60.0% (95% CI 25.3%-82.7%) for patients with Vp class 3, and 0.0% (95% CI 0.0%-0.0%) for patients with Vp class 4. Univariate analysis indicated that Vp class 4 was significantly associated with lower RFS compared with Vp class 0–2 (HR = 5.636, 95% CI 1.540–20.633, P = 0.0101). Other baseline characteristic, including gender, ECOG score (0 vs 1), CNLC stage (IIb vs IIIa)/BCLC stage (B vs C), HBV status (positive vs negative), HCV status (positive vs negative), tumor size (≥ 5 cm vs < 5 cm), number of tumors (2 vs 1 and ≥ 3 vs 1), pathology (macroscopic tumor thrombus vs none and microvascular tumor thrombus vs none), tumor capsule integrity (yes vs no), MVI score (M1 vs M0 and M2 vs M0), baseline AFP (≥ 400 ng/mL vs < 200 ng/mL and 200–400 ng/mL vs < 200 ng/mL), and preoperative AFP (≥ 400 ng/mL vs < 200 ng/mL and 200–400 ng/mL vs < 200 ng/mL), showed no significant association with RFS (Supplementary Table 1).

Multivariate analysis, including baseline AFP, showed that age (HR = 1.050, 95% CI: 1.000–1.102, P = 0.0497), ECOG score 1 (HR = 27.409, 95% CI: 1.286–584.180, P = 0.0339), and baseline AFP ≥ 400 (HR = 19.067, 95% CI: 1.674–217.211, P = 0.0176) were significantly associated with lower RFS, while other factors were not significant (P ≥ 0.05) (Supplementary Table 2). When preoperative AFP was included in the multivariate analysis, no factors were significantly associated with RFS (P ≥ 0.05) (Supplementary Table 3).

Multivariate stepwise regression analysis, including baseline AFP, showed that compared with Vp class 0–2, Vp class 4 (HR = 5.636, 95% CI 1.540–20.633, P = 0.0090) was significantly associated with lower RFS (Supplementary Table 4). Similarly, including preoperative AFP in multivariate stepwise regression analysis, Vp class 4 (HR = 5.687, 95% CI 1.552–20.836, P = 0.0087) remained significantly associated with lower RFS (Supplementary Table 5).

Table 2 Recurrence-Free Survival After Treatment

Variables	Values
RFS n (%)	
Event	28 (58.3%)
Censored	20 (41.7%)
Median (months, 95% CI)	16.1 (10.2, –)
6-month RFS rate (95% CI)	83.3% (69.4%-91.3%)
12-month RFS rate (95% CI)	60.4% (45.2%-72.6%)
24-month RFS rate (95% CI)	38.9% (24.6%-52.9%)

Abbreviation: RFS, recurrence-free survival.

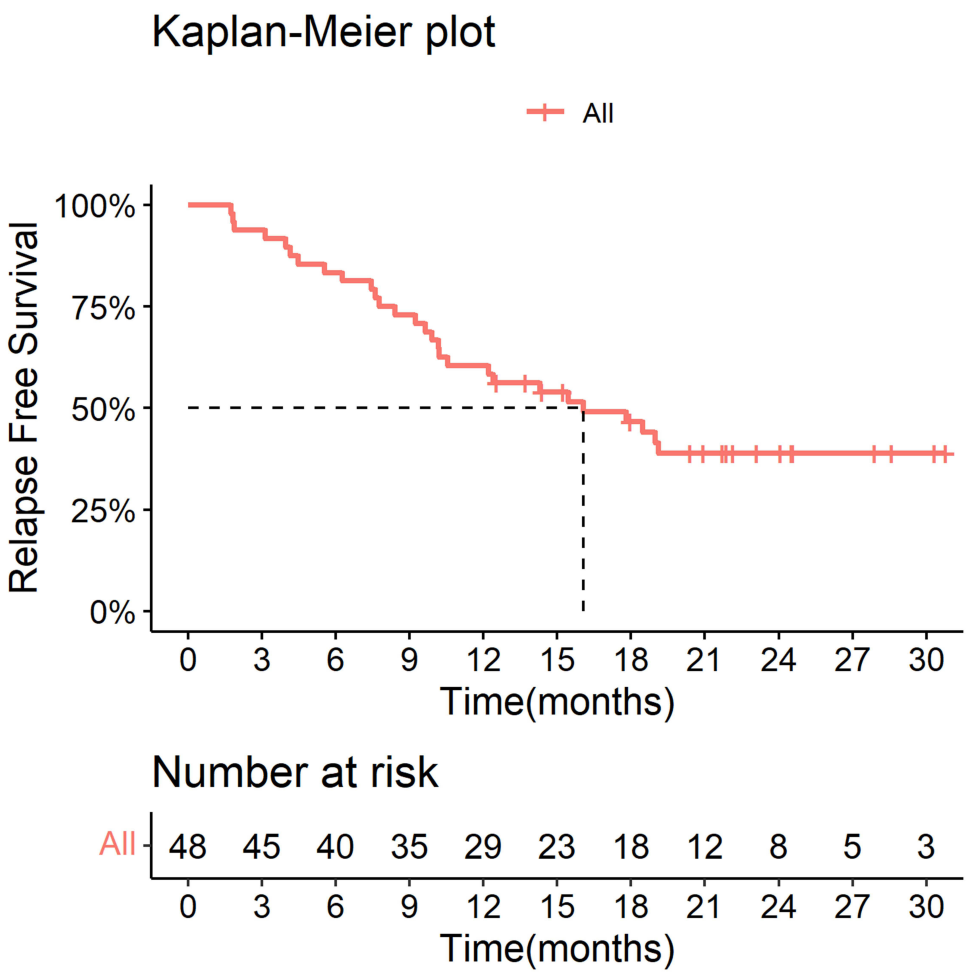

Figure 1 Kaplan-Meier Survival Curve of recurrence-free survival (RFS).

Based on the results of the univariate and multivariate analyses, age, ECOG score, Vp class, and baseline AFP were included in the COX regression model for multivariate analysis. The results suggested that Vp class 4 (HR = 5.415, 95% CI 1.464–20.037, P = 0.0114) was significantly associated with lower RFS, while other factors were not significant (P ≥ 0.05), as shown in Table 4. When age, ECOG score, Vp class, and preoperative AFP level range were included in the COX

Table 3 RFS by Vp Stratification

	Vp0-2	Vp3	Vp4	Stat	*P* Value
RFS n (%)					
Event	20 (57.1%)	5 (50.0%)	3 (100%)		0.3552
Censor	15 (42.9%)	5 (50.0%)	0		
Median (months, 95% CI)	17.8 (10.5)	(1.9)	7.6 (1.8, 9.2)		
6 months rate (95% CI)	88.6% (72.4%, 95.5%)	70.0% (32.9%, 89.2%)	66.7% (5.4%, 94.5%)		
12 months rate (95% CI)	65.7% (47.6%, 78.9%)	60.0% (25.3%, 82.7%)	0.0% (0.0%, 0.0%)		
24 months rate (95% CI)	39.1% (22.3%, 55.5%)	50.0% (18.4%, 75.3%)	0.0% (0.0%, 0.0%)		
HR VP 3 vs 0–2	0.899 (0.337, 2.401)				
HR VP 4 vs 0–2	5.636 (1.540, 20.633)				

Abbreviations: RFS, recurrence-free survival; Vp class, Liver Cancer Study Group of Japan portal vein tumor thrombus (PVTT) classification.

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Table 4 Multivariate Analysis (Selected Variables Including Baseline AFP)

Variable	HR (95% CI)	*P* Value
Age (years)		
≥ 65 / < 65	1.020 (0.978–1.063)	0.3583
ECOG score		
1 / 0	1.624 (0.507–5.206)	0.4143
Vp class		
3 / 0–2	0.914 (0.302–2.761)	0.8729
4 / 0–2	5.415 (1.464–20.037)	0.0114
Baseline AFP level (ng/mL)		
200–400 / < 200	1.476 (0.323–6.740)	0.6152
≥ 400 / < 200	0.830 (0.182–3.783)	0.8097

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Vp class, Liver Cancer Study Group of Japan portal vein tumor thrombus (PVTT) classification; AFP, alpha-fetoprotein.

regression model for multivariate analysis, Vp class 4 (HR = 5.034, 95% CI 1.326–19.111, P = 0.0176) was significantly associated with lower RFS, while other factors remained non-significant (P ≥ 0.05) (Table 5).

OS Rate

As of this analysis, a total of 7 patients (14.6%) of 48 died. The 12-month OS rate was 93.6% (95% CI 81.4%-97.9%), and the 24-month OS rate was 82.8% (95% CI 64.5%-92.2%) (Table 6). The median OS was not reached. The KM survival curve of OS is shown in Figure 2.

Univariate analyses of the impact of baseline characteristics on OS showed that gender, ECOG score, CNLC stage, Vp class, HBV status, HCV status, tumor size, number of tumors, pathology, HCC capsule, MVI, baseline AFP, and preoperative AFP had no significant association with OS (Supplementary Table 6).

Table 5 Multivariate Analysis (Selected Variables Including Preoperative AFP)

Variable	HR (95% CI)	*P* Value
Age (years)		
≥ 65 / < 65	1.018 (0.977,1.061)	0.3868
ECOG score		
1 / 0	1.503 (0.470,4.806)	0.4916
Vp class		
3 / 0–2	1.010 (0.344,2.970)	0.9851
4 / 0–2	5.034 (1.326,19.111)	0.0176
Preoperative AFP level (ng/mL)		
200–400 / < 200	1.134 (0.758,1.697)	0.5413

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Vp class, Liver Cancer Study Group of Japan portal vein tumor thrombus (PVTT) classification; AFP, alpha-fetoprotein.

Table 6 Overall Survival After Treatment

Variable	Values
OS n (%)	
Event	7 (14.6%)
Censored	41 (85.4%)
Median (months, 95% CI)	
6-month OS rate (95% CI)	
12-month OS rate (95% CI)	93.6% (81.4%, 97.9%)
24-month OS rate (95% CI)	82.8% (64.5%, 92.2%)

Abbreviation: OS, overall survival.

Safety

Among the 50 subjects included in the SS, 44 (88%) experienced TRAEs, with 7 (14%) having grade 3 or higher. Grade 3 and higher TRAEs included proteinuria in 3 subjects (6%), thrombocytopenia in 3 subjects (6%), leukopenia in 1 subject (2%), neutropenia in 1 subject (2%), elevated aspartate aminotransferase (AST) in 1 subject (2%), and elevated alanine aminotransferase (ALT) in 1 subject (2%). TRAEs occurring in more than 10% of the subjects included palmar-plantar erythrodysesthesia syndrome in 14 subjects (28%), diarrhea in 11 subjects (22%), hypertension in 11 subjects (22%), gingival bleeding in 7 subjects (14%), pharyngolaryngeal pain in 7 subjects (14%), voice alteration in 6 subjects (12%), thrombocytopenia in 5 subjects (10%), proteinuria in 5 subjects (10%), and alopecia in 5 subjects (10%). Four

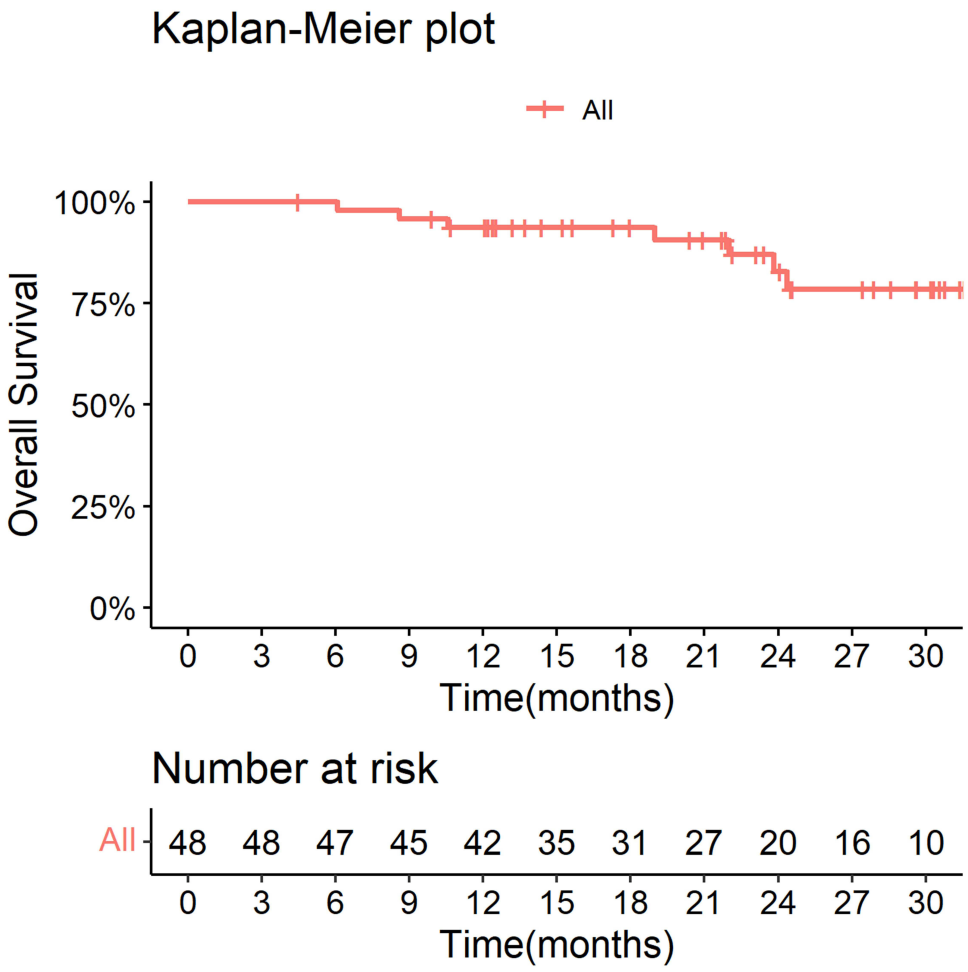

Figure 2 Kaplan-Meier Survival Curve of overall survival (OS).

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subjects (8%) had SAEs, including 1 subject with upper gastrointestinal bleeding, 1 with ascites and hepatic encephalopathy, 1 with biliary fistula, and 1 with Sjögren's syndrome, all of which were possibly or definitely unrelated to the drug. Three subjects (6%) experienced treatment interruption due to AEs, with all interruptions lasting less than 2 weeks. Nine patients (18%) had dose reduction due to AEs. No death or discontinuation was observed due to AEs. The incidence of TRAEs is detailed in Table 7.

Table 7 Treatment-Related Adverse Events (TRAEs)

TRAEs	Patients (n= 50)	
	All Grades, n (%)	≥ Grade 3, n (%)
Adverse event	44 (88.0%)	7 (14.0%)
White blood cell count decreased	3 (6.0%)	1 (2.0%)
Neutrophil count decreased	1 (2.0%)	1 (2.0%)
Lymphocyte count decreased	2 (4.0%)	0
Platelet count decreased	5 (10.0%)	3 (6.0%)
Gamma-glutamyltransferase increased	3 (6.0%)	0
AST increased	3 (6.0%)	1 (2.0%)
ALT increased	3 (6.0%)	1 (2.0%)
ALP increased	1 (2.0%)	0
Blood bilirubin increased	1 (2.0%)	0
Proteinuria	5 (10.0%)	3 (6.0%)
Urine white blood cell count increased	1 (2.0%)	0
Headache	3 (6.0%)	0
Pain in extremity	4 (8.0%)	0
Back pain	1 (2.0%)	0
Skin pain	1 (2.0%)	0
Arthralgia	4 (8.0%)	0
Omalgia	2 (4.0%)	0
Arthralgia in the fingers	1 (2.0%)	0
Ankle pain	1 (2.0%)	0
Right lower rib pain	1 (2.0%)	0
Knee pain	1 (2.0%)	0
Alopecia	5 (10.0%)	0
Hemorrhoidal rash	3 (6.0%)	0
Rash acneiform	2 (4.0%)	0
Palmar-plantar erythrodysesthesia syndrome	14 (28.0%)	0
Skin ulcer	2 (4.0%)	0
Pruritus cutaneous	1 (2.0%)	0
Periodontitis	2 (4.0%)	0
Gingival infection	1 (2.0%)	0
Angular stomatitis	1 (2.0%)	0
Mucositis oral	1 (2.0%)	0
Gingival bleeding	7 (14.0%)	0
Nose bleeding	1 (2.0%)	0
Pharyngolaryngeal pain	7 (14.0%)	0
Vomiting	1 (2.0%)	0
Esophagitis	1 (2.0%)	0
Decreased appetite	1 (2.0%)	0
Anorexia	1 (2.0%)	0
Gastralgia	3 (6.0%)	0
Gallstones	1 (2.0%)	0

(*Continued*)

Table 7 (Continued).

TRAEs	Patients (n= 50)	
	All Grades, n (%)	≥ Grade 3, n (%)
Ascites	1 (2.0%)	0
Abdominal distension	3 (6.0%)	0
Diarrhea	11 (22.0%)	0
Cyst	3 (6.0%)	0
Gallbladder stones	3 (6.0%)	0
Lower gastrointestinal hemorrhage	1 (2.0%)	0
Gastrointestinal discomfort	1 (2.0%)	0
Constipation	1 (2.0%)	0
Hypertension	11 (22.0%)	0
Voice alteration	6 (12.0%)	0
Insomnia	2 (4.0%)	0
Fever	1 (2.0%)	0
Palpitations	1 (2.0%)	0
Upper respiratory tract infection	1 (2.0%)	0
Micronodules in the lower lobe of the left lung	1 (2.0%)	0
Localized dissection of mesenteric artery	1 (2.0%)	0
Urinary tract infection	1 (2.0%)	0
Weight decreased	2 (4.0%)	0
Weight increased	1 (2.0%)	0

Abbreviations: TRAEs, treatment-related adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Discussion

Various strategies have been explored as adjuvant therapy to reduce recurrence rates. In Phase 3 STORM study, adjuvant sorafenib monotherapy for early-stage HCC (with > 61% of patients being Asian) at intermediate or high risk of recurrence did not show benefits in mRFS (33.3 months) compared to placebo (33.7 month).[13] Conversely, the phase 3 SOURCE study demonstrated that adjuvant sorafenib plus transarterial chemoembolization (TACE) significantly improved mPFS (16.8 month) and mOS (30.4 month) for Chinese HCC patients with portal vein tumor thrombosis (PVTT) showed significant improvement in compared to sorafenib alone (12.6 month and 22.5 month).[25] The phase 3 IMbrave050 study of adjuvant atezolizumab plus bevacizumab in high-risk HCC (> 83% BCLC stage A and > 81% Asian) initially showed improved 1-year RFS rate (78% vs 65%) compared to active surveillance.[15] However, with longer follow-up, this benefit was not sustained (median RFS: 33.2 vs 36.0 months; HR=0.90; 95% CI: 0.72–1.12), though some specific subgroups showed benefit.[16] Adjuvant donafinib combined with anti-PD-1 antibody in Chinese patients with stage A-B HCC and a high risk of recurrence showed a 1-year RFS of 80% in a Phase 1 study.[14] Adjuvant lenvatinib combined with TACE in Chinese HCC patients (> 42% BCLC stage C) with high risk of recurrence achieved significantly better 1-year DFS rate (60.5%) and mDFS (19.0 month) compared with TACE only (42.7% and 10.0 month) in LANCE study.[26]

In this single-arm Phase 2 study of lenvatinib as adjuvant monotherapy for CNLC stage IIb/IIIa HCC after radiologically confirmed R0 resection, the primary endpoint of 1-year RFS rate was 60.4%, an improvement from the reported 50.5% in the preliminary analysis for the same patients,[27] though it did not reach the hypothesized 70%. The mRFS was 16.1 months, consistent with the historically reported 16.5 months,[27] while the mOS was not reached at the time of this analysis. Our results align with the LANCE and SOURCE studies but differ from STORM, IMbrave050 and donafinib phase 1 studies, possibly due to the former studies recruiting HCC patients at intermediate-advanced stages, while the latter focused on early-stage HCC patients.

Although lenvatinib demonstrated non-inferiority to sorafenib in the first-line treatment of uHCC,[22] its potent inhibition of FGFR, unlike sorafenib, makes it particularly valuable in the adjuvant setting.[18] While VEGFR inhibition effectively blocks angiogenesis, lenvatinib's additional FGFR inhibition provides direct anti-tumor effects that are particularly relevant for suppressing residual micrometastases after surgery.[18] This is particularly important in high-risk patients, who are more likely to harbor micrometastases at the time of surgery. By simultaneously inhibiting VEGFR and FGFR pathways, lenvatinib is well-suited to prevent micrometastases from progressing into detectable recurrences.[28] The IMbrave-050 trial evaluated atezolizumab (anti-PD-L1) plus bevacizumab (anti-VEGF) as adjuvant therapy for HCC patients after curative resection or ablation. However, patients with autoimmune conditions face heightened risks of immune-related AEs with checkpoint inhibitors,[29] making lenvatinib a safer alternative. Additionally, immunotherapy can trigger graft rejection in liver transplant recipients,[29] a common subgroup among HCC patients, where lenvatinib serves as a viable option when atezolizumab is contraindicated. Moreover, oral administration of lenvatinib, along with its direct anti-tumor effects provide a faster initial response compared to the delayed benefits of immunotherapy.[30]

Postoperative recurrence may occur early or late, with early recurrence typically occurring within 2 years after surgery, and late recurrence happening at 2 years and beyond.[31,32] Risk factors for early recurrence include multiple tumors, longest tumor lesion diameter > 5 cm, poor differentiation (Edmondson grade III–IV), microvascular or major vascular invasion, lymph node metastasis, surgical margin ≤ 1 cm, and persistently abnormal tumor markers (AFP and/or abnormal prothrombin [des-gamma carboxyprothrombin, DCP]). Risk factors for late recurrence include age > 60 years, active chronic viral hepatitis, HBV DNA > 10^6 copies/mL, positive HBsAg, degree of cirrhosis, Ishak score > 6 or Scheuer > 4, hypoalbuminemia, and multiple tumors.[32–39] Patients at high risk of early recurrence should receive adjuvant therapy after surgery as appropriate. In this study, we analyzed the impact of various potential risk factors for recurrence on RFS and OS, including age, gender, ECOG score, CNLC stage, HBV status, HCV status, tumor size, number of tumors, pathology, tumor capsule integrity, MVI severity, baseline AFP, and preoperative AFP. Both univariate and multivariate regression analyses for RFS revealed that only Vp4 PVTT might be a risk factor for low RFS. Univariate analysis for OS showed no significant correlation with any factors. Previous literatures have also reported that PVTT is a high-risk factor for liver cancer recurrence.[40–42]

Regarding safety, although the median duration of lenvatinib treatment in this study was twice as long as in the REFLECT study (11.8 vs 5.7 months), the incidence rates were lower for terms of treatment-related treatment-emergent AEs (TEAEs) (88% vs 99%), treatment-related grade 3 or 4 TEAE of (14% vs 57%), serious treatment-related TEAE (8% vs 18%), TEAE leading to drug withdrawal (6% vs 9%), and TEAE leading to dose reduction (18% vs 37%). The safety profile of these two studies was comparable. Patients treated with lenvatinib experienced higher incidences (≥15%) of palmar-plantar erythrodysesthesia, diarrhea, and hypertension, and lower incidences of proteinuria, decreased PLT, and elevated AST. The incidence of decreased appetite was significantly lower in this study, while incidences of gingival bleeding and throat pain were relatively high. These slight differences in incidence rates may be attributed to the limited sample size of this study.

There are some limitations to note in the present study. Firstly, it was a single-arm exploratory trial lacking a control group or randomization, and the sample size may have limited the statistical power of subgroup analyses. This may explain the non-significant findings for certain risk factors (eg, tumor size ≥ 5 cm, microvascular invasion), despite Vp4 PVTT being associated with RFS, underscoring the need for confirmation in randomized controlled trials. Secondly, the OS data were immature, and longer follow-up is needed to assess the survival benefit of lenvatinib in HCC patients. Finally, the variability in the time from hepatectomy to enrolment (0.07–2.53 months) may introduce bias, as it exceeded the 6-week protocol limit due to COVID-19 but it unlikely to affect our study's conclusions, as IMbrave050 allows enrollment 4–12 weeks post-surgery.[15] Despite these limitations, our results revealed a higher 1-year RFS rate, suggesting that larger studies with standard-of-care controls are warranted to evaluate adjuvant lenvatinib monotherapy for CNLC stage IIb/IIIa HCC.

Conclusions

Adjuvant lenvatinib was associated with higher 1-year RFS rate compared with historical report for patients with CNLC stage IIb/IIIa HCC after R0 hepatectomy. This promising result, combined with a consistent safety profile similar to previous studies, suggests that lenvatinib monotherapy may represent an effective and safe adjuvant treatment option.

Data Sharing Statement

The data presented in this study are available from the corresponding author on reasonable request.

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Disclosure

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